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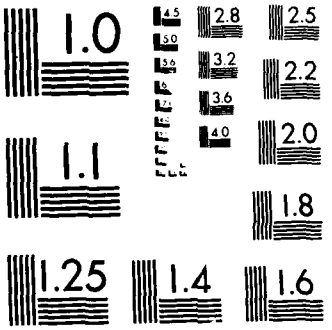

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We investigated the stability of adult cerebral motor cortex organization by comparing cortical motor representation patterns in rats with a motor nerve lesion to normal rats. Eight days after section of the facial motor innervation of the whisker follicles, cortical mapping with electrical stimulation showed that eye, eyelid, or forelimb movements could now be evoked at low thresholds from the region of the normal vibrissa representation. This indicates that adjacent representations expand into the deefferented area. These changes suggest that cortical motor representations depend upon the integrity of peripheral targets for long-term maintenance.

Adult Motor Cortex Somatic Representation Patterns Reorganize after Motor Nerve Injury

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Abstract. We investigated the stability of adult cerebral motor cortex organization by comparing cortical motor representation patterns in rats with a motor nerve lesion to normal rats. Eight days after section of the facial motor innervation of the whisker follicles, cortical mapping with electrical stimulation showed that eye, eyelid, or forelimb movements could now be evoked at low thresholds from the region of the normal vibrissa representation. This indicates that adjacent representations expand into the deefferented area. These changes suggest that cortical motor representations depend upon the integrity of peripheral targets for long-term maintenance.

The primary motor area of the cerebral neocortex (MI) is involved, either directly or through subcortical linkages, in the flexible and skilled control of somatic musculature (1). Lesions or damage of MI inputs or outputs compromise skilled motor performance and other motor functions (2); in some cases functional deficits recover with time, but aberrations in motor control may persist or worsen (3). The mechanisms that underlie either recovery or normal acquisition of skilled motor behavior are presently unclear. Recently, we observed that rats receiving a peripheral nerve injury as neonates developed an MI representation pattern that differed markedly from that of normal rats (4). When MI developed in the absence of peripheral innervation of the limb, certain of the intact somatic representations in MI were larger than normal. These alterations in MI representation patterns, similar to those observed in the somatic sensory cortex of adult mammals (5), could mediate alterations in motor functions following learning or disease. Nevertheless, it is uncertain whether representation patterns in adult MI continue to be mutable. If they do change, it is unknown whether MI reorganization could be considered as a substrate for either recovery of function or acquisition of motor skills in mature animals. The current investigation was intended to determine whether somatotopic representations in MI of adult rats are modified following a peripheral motor nerve lesion.

The organization of MI was studied in 8 normal rats and in 7 rats that had the motor innervation of the right mystacial vibrissa transected when the animals were mature. The buccal and marginal mandibular branches of the right facial nerve were ligated and transected (*6*). The experimental animals were allowed to recover for 8 days to 4 months and then the left MI and adjacent cortex were mapped with intracortical microstimulation techniques (*7*). In the normal rats, we defined MI as the region of frontoparietal cortex in which low intensity (≤60 μA) electrical stimulation evoked movement (*8*). A similar cortical expanse was mapped in the experimental animals. At each electrode penetration site, the body part that was activated at the lowest current intensity was identified by visual inspection and muscle palpation. The thresholds for all body parts activated at currents up to 60 μA were noted.

The low threshold stimulation maps of MI for one normal and one experimental rat are shown in Fig. 1. In normal rats, MI is typically segregated into distinct zones containing the representation for the forelimb, hindlimb, jaw, eyelid, eye, vibrissa, jaw and tongue and neck or trunk (*9*). The area from which eyelid or eye movements were evoked is located approximately in the medial 1.75 mm of frontal agranular cortex; the eyelid/eye area is laterally contiguous with the vibrissa representation, which in turn is laterally contiguous with the forelimb and axial body representations. In some normal animals (3 of 7), the eyelid/eye and forelimb representations appeared to have a short boundary, since movements of these body parts could be elicited from penetrations separated by ≤500 μm. The vibrissa area is interposed between, and therefore separates, most of the eyelid/eye and forelimb representations. Normally, the MI vibrissa field extends from about 0.0 to 3.0 or 4.0 mm anterior to bregma and from about 1.5 to 2.5 mm lateral from the midline. Threshold stimulation in the MI vibrissa representation of the normal rats predominantly yielded movements of several contralateral vibrissa, though sites with concurrent movement of contralateral and ipsilateral vibrissa movement were also observed.

In the 8 normal rats, a total of 125 penetrations was within the low threshold vibrissa representation. Stimulation at 32 percent (n = 40) of these sites evoked only vibrissa movements. In the remaining 68 percent (n = 85) of the sites other movements, in addition to the vibrissa movements, were evoked at the same or higher currents. In the sample of "coincident" movement sites, there were 50 sites from which eyelid/eye movements and 25 sites from which forelimb movements were evoked coincidentally with vibrissa movements. These coincident sites were most typically located near the borders between the low threshold vibrissa area and areas where other body parts were represented.

Facial nerve transection could have produced a zone in MI from which stimulation could not evoke movement. We found no evidence for a greater than normal preponderance of negative sites within this region. Instead, stimulation in the region of the normal vibrissa representation evoked eyelid, eye, forelimb or, less frequently, ipsilateral vibrissa movements at low thresholds. Moreover, the ipsilateral vibrissa representation (clear area in middle of Fig. 1B) was considerably

smaller than the total vibrissa region in MI of the normal rats, and in some cases (n = 2) a separate ipsilateral vibrissa zone could not be identified at all. Unlike in the normal rats, the low threshold eyelid/eye and forelimb areas shared an extensive border in the anterior-posterior dimension, indicating that one or both of these representations had expanded into the former vibrissa territory. Some of the features of expanded MI representations from the normal and experimental rats are compared in Fig. 2. The low threshold eyelid/eye sites (Fig. 2A), as measured by the number of sites at specific lateral distances from the midline, were distributed more laterally and the forelimb sites (Fig. 2B) were found more medially in the experimental rats. This shift was also evident in the lateral (eyelid/eye, Fig. 2C) and medial (forelimb, Fig. 2D) shift of the modes of these two distributions.

The coincidence of eyelid/eye and forelimb movements at single MI sites in the normal and experimental rats further illustrates expansion of adjacent representations into the vibrissa area. In the normal animals, stimulation at current levels up to 60 μA evoked movements of eye or eyelid and forelimb coincidentally at only 8 of a total of 242 (3.3 percent) electrode penetration sites from which either eyelid/eye or forelimb movements were evoked. These coincident sites were observed in only 3 of the 8 normal animals. In the experimental animals there were 34 coincident eyelid and forelimb sites from a total of 274 (12.4 percent) sites from which either forelimb or eyelid/eye movements were evoked. All experimental rats had at least one site (4.86 ± 1.12 sites, mean, ±SEM) from which both eyelid/eye and forelimb movements were evoked. Comparable changes in border apposition and paired forelimb and eyelid/eye movements were observed at the shortest and longest survival times.

We also examined the currents necessary to evoke movements in the MI as another measure of cortical reorganization. The lowest current necessary to evoke movements of the eyelid or eye and the forelimb was compared in the normal and experimental rats (*10*) to examine the potential function of expansion of MI body representations. In the normal rats, the mean low threshold current needed to evoke eyelid/eye movements was 29.63 ±1.33 μA (n = 102 sites) and the representation extended from 0.75 to 2.0 mm lateral from the midline (Fig. 2C). In the

experimental animals, the low threshold representation for eyelid/eye movements extended laterally to 2.75 mm with a mean current of 24.83 ±1.05 μA (n = 128), which was significantly lower than for the normal animals ($P \leq 0.005$, t test). In the normal rats, the low threshold forelimb zone extended medially to 2.0 mm (Fig. 2D) with a mean current of 24.35 ±1.03 μA (n = 82) and in the animals with a facial nerve transection the low threshold forelimb zone extended medially to 1.5 mm with a mean current of 25.07 ± 1.08 μA (n = 122). Thus, the forelimb area in the experimental rats had the same strength of connection as in the normals.

The present results show that there is a dynamic organization of MI representation patterns. Novel movements are evoked in the region of the normal vibrissa representation following transection of the motor facial nerve innervating the vibrissa in adult rats apparently by the expansion of adjacent representations into the vibrissa area. This expansion is supported by three findings. First, there are no large areas in MI from which movements cannot be evoked. Second, there is an increased probability of evoking forelimb and eyelid/eye movements at the same MI site. Third, the forelimb and eyelid/eye representations share an elongated boundary. An interpretation of these findings is that motor nerve lesions only reveal occult representations within MI. Thus, for example, if eyelid or eye movements were already represented within the normal vibrissa area, removal of the low threshold vibrissa area would simply uncover the eyelid/eye representation as the low threshold movement in that region. However, the presence in normal MI of sites from which only vibrissa movements can be evoked, the lack of silent zones in experimental MI and the increased coincidence of forelimb and eyelid/eye movements after nerve lesions argue against a simple uncovering of already existing representations. Therefore, we conclude that new connectional relationships are formed by the MI vibrissa area following motor nerve lesions in adult rats.

The present results complement our earlier studies on newborn rats that showed a similar form and extent of change in MI (*4*). Though those nerve lesions were made when the motor cortex was immature, the similarity of lesion effect in newborn and adult rats suggests that comparable mechanisms may operate for the development and maintenance of MI representation

patterns. Lesions in our earlier studies included both sensory and motor nerves; we now have found that transection of a motor nerve, that necessarily removes an ultimate target organ for MI but does not explicitly remove an input to MI, is a sufficient condition to induce MI reorganization.

Two mechanisms seem plausible to explain MI reorganization following motor nerve transection. The first would constitute growth or "sprouting" of neuronal processes to form new connections in the periphery or in the CNS. The sprouting of the transected facial motor neuron axons into circumorbital musculature could account for the expansion of the eyelid/eye representation. Inspection of the facial nucleus from our cases indicates that many whisker motor neurons survive for months after axotomy, and these cells could form new peripheral connections. However, the time necessary for peripheral axonal sprouts to form new functional connections is not consistent with the rate of reorganization that we observed (*11*). There is currently substantial evidence that collateral axonal sprouting occurs within the CNS and that the rate of sprouting appears sufficient to account for MI reorganization within 8 days (*12*). It is possible then that following facial nerve transection the acute and chronic changes occurring within the neurons innervating the vibrissa musculature (*13*) stimulate the presynaptic terminals to contact new targets, some of which are the motor neurons innervating the eyelid muscles. Whereas this mechanism has some parsimony for expansion of the eyelid representation, the expansion of the forelimb representation, which would most likely require axonal sprouting from the brain stem to the cervical enlargement of the spinal cord, might not be explicable on the basis of subcortical sprouting. An alternate mechanism of unmasking would constitute activation of already existing synapses that are normally weak or silent but become strengthened after motor nerve lesion. Unmasking-like phenomena have been shown to exist and act in the CNS over fairly rapid time courses (*14*). Although unmasking might occur at any of the synaptic relays between MI and the motor neurons, it would require that cells have relatively widespread axonal projections and that only certain of the connections be normally active. This criterion could be met, for example, by those pyramidal tract neurons that have broadly distributed collaterals, some of which appear to project to widely separated motor neuron pools (*15*). Still, the functional state of synapses formed

by these collateral axons remains unclear. A similar mechanism of activation of normally silent synapses might occur within MI. In this case, MI reorganization could occur within specific MI intracortical circuits that have been recently described (*16*). Such horizontal projections might interconnect different MI representations and form the basis for expansions of intact representations into deefferented areas.

Despite our inability to determine a mechanism by which MI reorganization occurs, it was clear that some aspects of the functionally reorganized MI appeared normal. That is, the types of movements that were evoked and the threshold currents that were required to evoke movement in the newly reorganized cortex were similar to those obtained from more traditionally located body representations. Thus, it is possible that newly organized cortex has functional properties, in terms of movement control, similar to those found in normal representations in MI. The strength of the synaptic pathway between the new zones of eyelid/eye and forelimb representations in MI and motor neurons of the experimental rats appeared to be similar to, or stronger, than that between comparable zones in MI and motor neurons in the normal rats. *Synaptic strength* in this instance is defined as the current required to evoke movement between MI and target muscles, with lower currents indicating a stronger effective connection. The behavioral significance of MI reorganization in adult animals following a peripheral motor nerve injury remains unclear. Although more cortical territory became related to movement of a body part it is not necessarily correct to assume that larger representations in MI imply improved function; however, this does appear to be the case for larger representations in the somatic sensory cortex (*17*). Analysis of the cellular properties and the concomitant behavioral performance after peripheral injury would be required to determine the extent to which reorganized MI contributes to normal or abnormal function.

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6. The buccal and marginal mandibular branches of the right facial nerve were transected surgically during ketamine hydrochloride anesthesia (100 mg/kg). These branches carry motor axons that innervate the muscles attached to the vibrissa and there are no sensory fibers in these branches of the facial nerve; K. Semba and M. D. Egger *J. Comp. Neurol.* **247**, 144 (1986). After transection the distal and proximal ends of the nerve were ligated with silk suture. The wound was sutured closed, and after recovery from anesthesia the animal was returned to the home cage.
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Reed, in *Motor Control Mechanisms in Health and Disease*, J. E. Desmedt, Ed. (Raven Press, New York, 1983), *Advances in Neurology*, vol. 39, p. 347. The acute mapping procedures have been described previously; J. P. Donoghue and S. P. Wise, *J. Comp. Neurol.* **212**, 76 (1982). Briefly, animals were anesthetized with ketamine hydrochloride (intraperitoneal injections, 100 mg/kg) and mounted in a stereotaxic frame. Microelectrodes (glass insulated, PtIr, 0.5-2 MΩ impedance at 1 KHz) were lowered to a depth of 1.8 ±0.1 mm below the pial surface. Current trains (30 msec duration, 300 Hz, 200 μsec monopolar, cathodal pulses) of 5-60 μA were passed through the electrode tip while we examined the body visually and by touch to determine which body parts moved or which muscles contracted. The resolution of the electrode penetrations was between 0.1-0.5 mm. At the termination of each experiment, lesions were made at selected sites by passing 10 μA DC through the electrode tip for 10 sec. The animals were perfused, and the brains were removed and processed for histological localization of penetration sites.

8. Maps were constructed by plotting penetrations sites on a surface view of the cortex. Each body part representation was defined as the region that enclosed the cortical area where movement of that body part was evoked at the lowest current intensity. Map borders were defined as the mid-point between penetrations evoking movements of two separate body parts (e.g., whiskers and forelimb) at the lowest threshold. However, boundaries were drawn through points where movement of two body parts were evoked at similarly low thresholds (within ±2 μA of the lowest threshold movement at that site), unless the points were separated by more than 1 mm. In that case boundaries were drawn 250 μm from the data point. The total representation for a body part often extends beyond the low threshold representation, but in this extended zone, which is most often contiguous with the low threshold zone, movement of other body parts are evoked at lower currents. Movement of body parts in the extended zones could reflect a functional overlap of two or more representations or might be related to current spread into the contiguous low threshold zone.

9. The primary motor cortex is defined in a variety of mammals as the cerebral neocortical area in which movements can be evoked at the lowest levels of electrical stimulation; C. N. Woolsey, in *The Biological and Biochemical Bases of Behavior*, H. F. Harlow and C. N. Woolsey, Eds. (Univ. of Wisconsin Press, Madison, 1958), p. 63. In rats intracortical stimulation mapping with low intensity currents reveals a topographically ordered pattern of representation in MI such that focal sites in cortex are related to one or a few closely related muscles; R. D. Hall, E. P. Lindholm, *Brain Res.* **66**, 23 (1974); K. J. Sanderson, W. I. Welker, G. M. Shambes, *ibid.* **292**, 251 (1984); E. J. Neafsey et al., *Brain Res. Rev.* **11**, 77 (1982).

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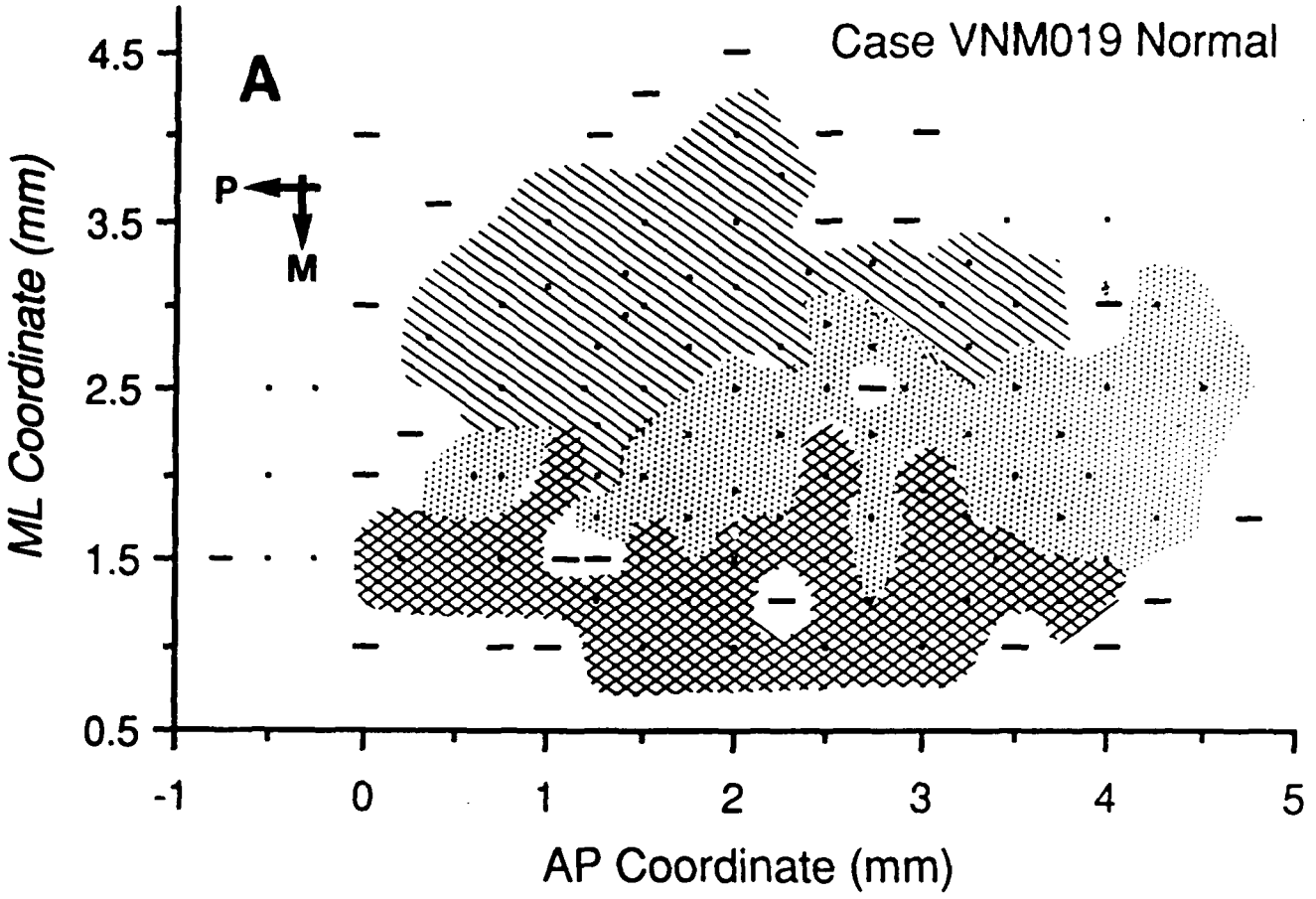
Figure Legends

Fig. 1. Microstimulation maps of MI in one control and one experimental rat. In each section, a dot marks a stimulation site from which movements were evoked and a dash mark a site from which no movement could be evoked at currents up to 60 μA. (A) Pattern of representation at the lowest current intensities showing the location of the forelimb (hatched area), vibrissa (stippled area) and eyelid/eye (cross-hatched area) representations in MI of a normal rat. (B) Low threshold map from an experimental rat, showing zones from which movements of the forelimb (hatched area), eyelid/eye (cross-hatched area) and ipsilateral vibrissa (clear region between the forelimb and eyelid/eye areas) are evoked at the lowest currents. Note that the forelimb and eyelid/eye areas are separated by the vibrissa representation in the normal animal but are contiguous throughout most of the anterior—posterior extent of MI in the experimental animals.

Fig. 2. Comparisons of the distribution of the medial—lateral distribution of eyelid/eye and forelimb sites in normal and experimental rats. (A and B) The proportion of low threshold sites for eyelid/eye (A) and forelimb (B) are plotted in relation to the medial—lateral coordinate of the penetration site. The graphs were constructed by taking all of the low threshold sites for eyelid/eye (left) or forelimb (right) movement across all control and experimental rats and then grouping the sites according to distance lateral from the midline, irrespective of anterior—posterior location. The percentage of low threshold sites in each 0.5 mm segment of MI was then plotted. The modal bin of the eyelid/eye representation is at located 1.5 mm lateral in normal rats but is located at 2.0 mm in experimental rats, and the eyelid/eye representations extends further lateral in experimental rats than in normal rats. On the other hand, the forelimb zone is more medially located in experimental rats than in normal rats. (C and D) Low threshold currents versus medial—lateral coordinate. All eyelid/eye (C) and forelimb (D) sites from control and experimental rats were averaged separately, and the mean current (±SEM) required to evoke movement at each 0.5 mm medial—lateral bin was plotted. Within a body representation, the mean low threshold currents

remained roughly constant. In experimental rats, the low threshold zone for the eyelid/eye expands laterally and the comparable zone for the forelimb expands medially.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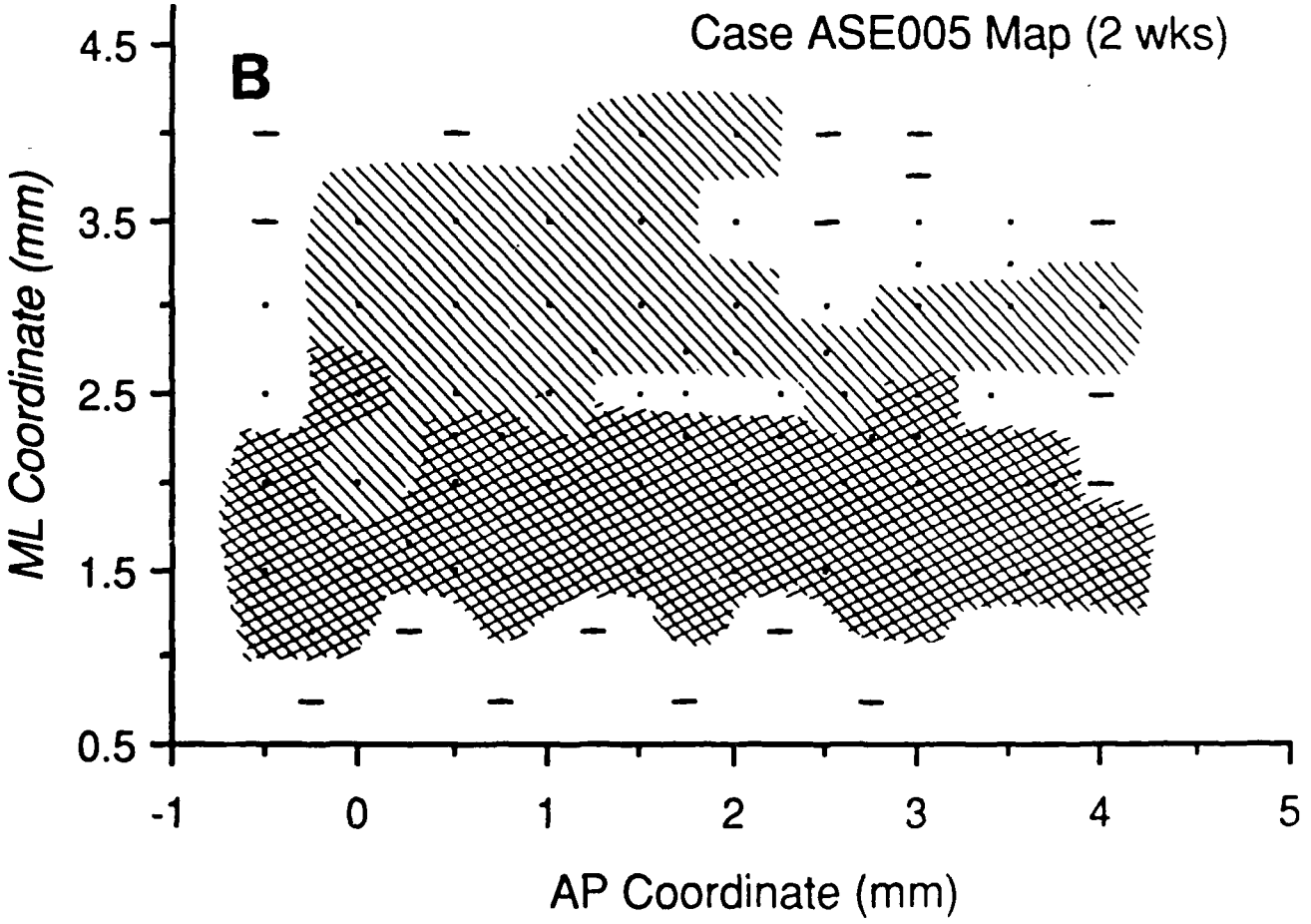
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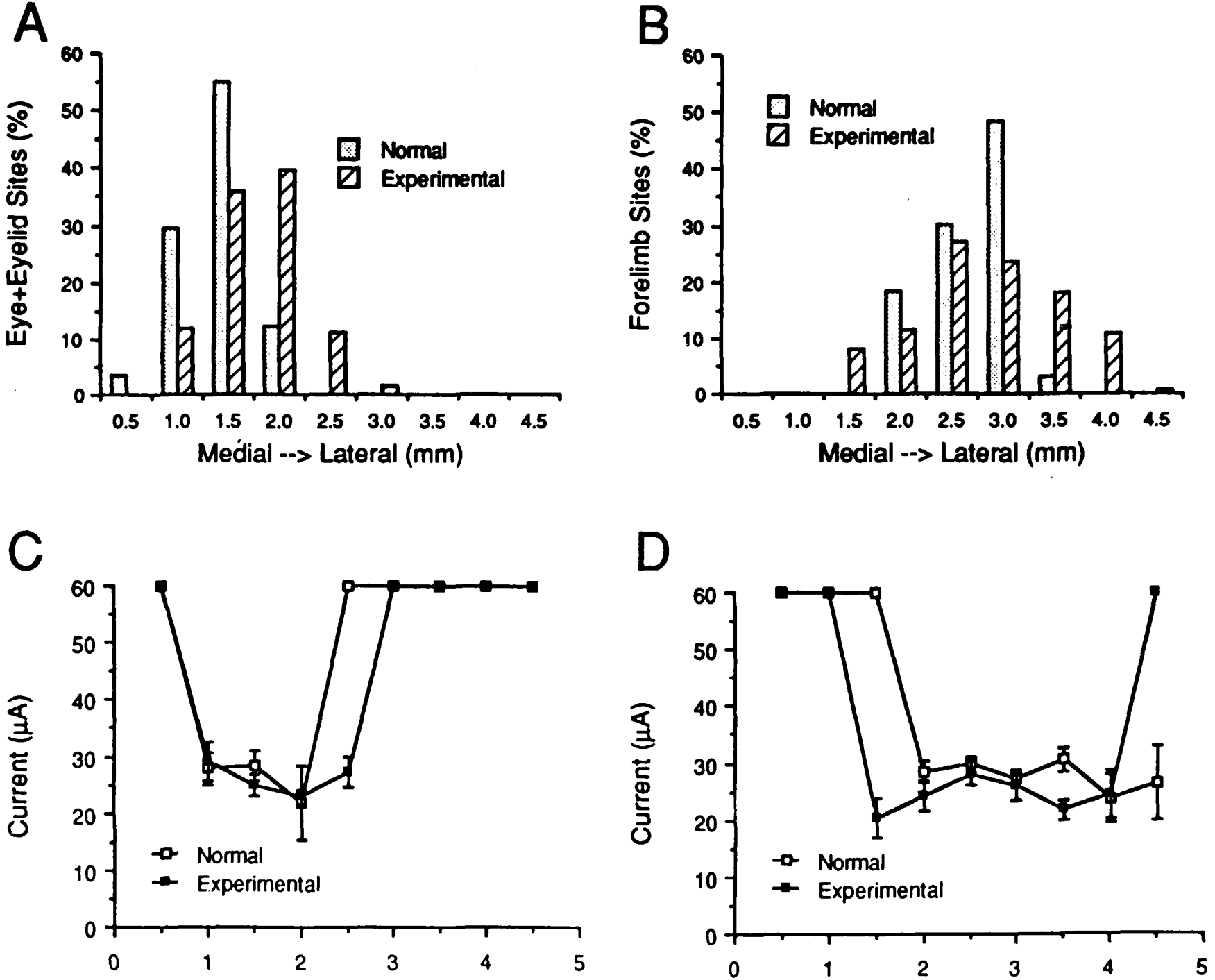
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